Liver Transplantation-associated Hypercalcemia Followed by Acute Renal Dysfunction

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Abstract

A 34-year-old woman with liver insufficiency due to glycogen storage disease III underwent a living spousal liver transplantation. Soon after the successful operation, moderate hypercalcemia along with hyperbilirubinemia emerged without clarified reasons. The hypercalcemia persisted for over a month despite calcitonin treatment and the serum calcium level surged to 13.2 mg/dl with albumin correction. Renal dysfunction was indicated by an acute increase in serum creatinine (≈0.8 to ≈2.8 mg/ml), which was assumed to be hypercalcemia-induced and was effectively treated with bisphosphonate, pamidronate (30 mg, i.v.). Recent topics related to transplantation-associated hypercalcemia are discussed.

Key words: liver transplantation, hypercalcemia, acute renal failure, immunosuppression, osteoclastogenesis, RANK, RANK-L

Case Report

The patient, a 34-year-old woman, was first diagnosed by liver biopsy with glycogen storage disease (GSD) type IIIb (Cori’s disease) at the age of 1.5 years old. She had been conservatively treated throughout her development, while the liver damage progressed and the diagnosis of liver cirrhosis was made at 23 years old. Examinations revealed portal hypertension, splenomegaly, liver tumor, and esophageal varices. Muscular involvement was indicated by electromyography and mild glycogen storage revealed by muscle biopsy, which suggested that the disease was to be re-categorized as type IIIa that accompanies a defect in the glycogen-debranching enzyme in muscle as well. While waiting for a cadaveric liver transplantation, the hepatic dysfunction developed further to insufficiency. About a year later, she was hospitalized at Nagoya City University Hospital for a living unrelated liver transplantation from her healthy husband. On admission, she was suffering from liver cirrhosis (asparate aminotransferase 51 U/l, alanine aminotransferase 2,120 U/l, choline esterase 64 U/l), profuse ascites with hypoproteinemia (total protein 5.0 g/dl, albumin 2.5 g/dl), icterus with hyperbilirubinemia (5.0 mg/dl), splenomegaly with pancytopenia (leukocyte 1,700/μl, erythrocyte 236×10^12/μl, hematocrit 26.3%, hemoglobin 8.9 g/dl, platelet 19,000/μl), and skeletal muscle damage with a high creatine kinase level (2,120 U/l) and normal exercise electrocardiogram. Her renal function was suggested to be normal (blood urea nitrogen 7 mg/dl, creatinine 0.4 mg/dl). Serological tests for hepatitis B and C were negative.

The recipient liver was removed and a graft weighing 465 g (37.3% of the estimated recipient liver mass) from the left lobe of the donor liver was successfully transplanted. Pathological examination of the excised liver revealed mild inflammation and, in a macroscopically white 10×15 mm nodule, moderately-differentiated hepatocellular carcinoma with microscopic vascular invasion. Immunosuppression therapy using cyclosporine and corticosteroids were started as shown in Fig. 1.

Headache and hypertension (systolic pressure ≈160 mmHg) appeared on the 2nd day posttransplant. The trough level of cyclosporine that had been close to simulation until the 2nd day posttransplant surged on the 3rd day posttransplant (391 ng/ml) and was difficult to control. On the 5th day posttransplant, asparate and alanine aminotransferase levels surged to 1,340 U/l and 379 U/l, respectively. Ultrasonography assured fair blood flow in the portal vein. Acute rejection was suspected and methylprednisolone sodium succinate (350 mg) was administered intravenously. Consequently, the surged aminotransferase levels tended to ameliorate in 6 hours. Mild renal dysfunction, in parallel,
was indicated by elevated levels of serum blood urea nitrogen (33 mg/dl) and creatinine (1.2 mg/dl), which was associated with a high cyclosporine level. To further manage the critical situation, an appropriate amount of steroids and mycophenolate mofetil were employed and tacrolimus hydrate was started on the 13th day posttransplant (Fig. 1), substituting for hard-to-control cyclosporine that is reported to cause bile congestion in a high dosage in animals. Related to the hypertension, hypomagnesemia was corrected using magnesium sulfate and the concentration was controlled within normal range (1.9 mg/dl as max on the 8th day posttransplant). When the hypercalcemia started to deteriorate despite calcitonin treatment as shown in Fig. 1, the magnesium level dropped from 1.8 on the 33rd day to 0.9 mg/dl on the 44th day posttransplant. Further correction lead to an almost normal level of magnesium (~2.5 mg/dl) on the 47th day posttransplant. An infection of cytomegalovirus (CMV), confirmed by the horseradish peroxidase-labeled monoclonal antibody, was suspected to partly explain the liver dysfunction, as preoperative serological tests for CMV had been negative. Ganciclovir and anti-CMV high-titer gamma-globulin were used from the 15th to 24th day posttransplant. Liver biopsy on the 15th day posttransplant, however, revealed minimal rejection, minimal inflammation, no hepatic necrosis, no congestion, and no atypical cells suggestive of CMV infection.

Figure 1. Temporal relationships of serum levels of calcium, creatinine, total bilirubin, and use of immunosuppressants, calcitonin, and pamidronate. cCa, corrected serum calcium level by the following equation: cCa = serum Ca level - serum albumin level + 4 (mg/dl). Until discharge, both serum creatinine and cCa remained stable and the total bilirubin level gradually decreased (1.9 mg/dl on the 128 day posttransplant, one week before discharge).
Moderate hypercalcemia (11–12 mg/dl, corrected by serum albumin level) and noted hyperbilirubinemia emerged after the operation, as also depicted in Fig. 1. The total bilirubin level peaked on the 24th day posttransplant (27.4 mg/dl) and gradually lowered. Table 1 shows laboratory findings which ruled out some of the frequent causes of hypercalcemia: hyperparathyroidism, malignancy, vitamin D toxicity, and familial hypocalciuric hypercalcemia. Intact parathyroid hormone (PTH), parathyroid hormone related peptide (PTH-rP), and 1 alpha 25 (OH)₂D₃ were not elevated. Serum osteocalcin, a bone metabolic marker, was also normal. Calcitonin therapy was started and continued, but there was no apparent response (Fig. 1). The persistent hypercalcemia aggravated and peaked at 12.3 mg/dl (serum albumin 3.1 g/dl) on the 41st day posttransplant, when the calcitonin therapy was suspended and the disodium pamidronate (30 mg) was administered intravenously.

Acute renal dysfunction was indicated by the surging serum creatinine level, which followed the development of hypercalcemia and peaked on the 44th day posttransplant (2.8 mg/dl). A single dose of pamidronate normalized the plasma calcium concentration within a week and also suppressed the elevated serum creatinine level. These changes also seemed to coincide with the liver dysfunction indicated by the serum total bilirubin level (Fig. 1).

Discussion

Deficiency of the glycogen-debranching enzyme is causative of glycogen storage disease (GSD) type III, a rare autosomal recessive disorder of glycogen metabolism. The possible development of hepatocellular carcinoma and/or hepatic failure makes these GSDs potential candidates for liver transplantation. Liver transplantation, however, is hampered worldwide due to the serious shortage of cadaveric organ donations. Living donor transplantation with the excellent outcomes has been ethically and socially accepted and is performed in many hospitals in Japan.

Hypercalcemia is a rare complication of advanced chronic liver disease without hepatoma. In the present case, the frequent causes for hypercalcemia were not evidenced by laboratory findings. While urinalysis showed decreased tubular phosphate reabsorption (Table 1), hyperparathyroidism was rejected by a normal level of serum PTH. In addition, urinary calcium excretion was rather increased, which ruled out hypocalciuric hypercalcemia. The hepatoma revealed by the post-operative pathology report could not explain hypercalcemia with serum PTH-rP below the cut-off level, especially after total extirpation of the native liver. However, it could partly explain the moderate hypercalcemia seen prior to the transplantation. Vitamin D toxicity was not induced by the perisurgical administration of vitamin supplements, since the serum level of 1,25(OH)₂D₃ was normal. Liver transplantation requires a patient to be bedridden for a long time per se. Prolonged immobilization is known to cause bone dissolution with hypercalcemia, hypercalciuria, elevated renal phosphorus threshold, and a decreased level of plasma 1,25(OH)₂D₃ (1), which seems to be in accordance with the laboratory examinations in the present case. However, we will not attribute the pathogenesis to immobilization, considering that the hypercalcemia developed within just one day post operation. The use of diuretics may lead to hypercalcemia by exerting hypocalciuric actions (2), which was not seen in the present case. It is known that the restoration of decreased intracellular magnesium is necessary for correcting hypocalcemia and can further induce hypercalcemia in chronic renal failure (3, 4). In the present case, the serum magnesium level that tended to decrease after the operation was corrected using magnesium sulfate throughout the treatment of hypercalcemia. Although the hypercalcemia was aggravated, the magnesium level actually decreased as previously described. Thus, we assume that magnesium played just a marginal role in the calcium metabolism modulation, if any.

Another noticeable aspect was the severe hyperbilirubinemia that occurred with the prolonged hypercalcemia after transplantation. A small-for-size liver graft of 40% or less is a known factor for persistent hyperbilirubinemia after a living-related liver transplantation (5). Gerhardt et al reported that hypercalcemia is a possible complication in advanced chronic liver disease, even if it were not for the hepatoma, and that it often accompanies mild to moderate renal dysfunction suggested by an elevated serum creatinine level (6). To our knowledge, however, the hypercalcemia that emerged after posttransplant liver failure has not been described to date and should be examined with special care in the future.

Post-transplantation bone disease is well recognized in renal transplantation, as well as in heart, lung, and liver transplants (7–12). It has been chiefly attributed to altered calcium metabolism and bone turnover induced by multifactorial side effects of corticosteroid treatment for rejection prevention (13) and, in renal transplantation, secondary hyperparathyroidism. Cyclosporine, an immunosuppressant that inhibits T cell activation and transcription of interleukin-2, is also reported to affect calcium balance. A study demonstrating that T-cell-deficient male nude rats were insusceptible to cyclosporine-induced osteopenia

**Table 1. Laboratory Data Related to Calcium Metabolism**

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal range</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine calcium (g/day)</td>
<td>0.1–0.3</td>
<td>0.39</td>
</tr>
<tr>
<td>FECa (%)</td>
<td>1–2</td>
<td>6.0*</td>
</tr>
<tr>
<td>%TRP</td>
<td>85–98</td>
<td>55*</td>
</tr>
<tr>
<td>Serological tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact PTH (pg/ml)</td>
<td>10–65</td>
<td>39</td>
</tr>
<tr>
<td>PTH-rP (pM)</td>
<td>&lt;0.6</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>1,25(OH)₂D₃ (pg/ml)</td>
<td>20–60</td>
<td>3.7</td>
</tr>
<tr>
<td>Osteocalcin (ng/ml)</td>
<td>2.9–12.3</td>
<td>3.1</td>
</tr>
</tbody>
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*suggests a value out of normal limits. FECa, fractional excretion of calcium. TRP: tubular reabsorption of phosphate.
strongly suggested the involvement of T cells in the altered bone turnover (14). The effect of cyclosporine on calcium metabolism, however, is rather controversial. Cyclosporine has been suggested to work beneficially, with its steroid-sparing effect, in bone remodeling through increasing serum concentrations of 1,25-(OH)₂-vitamin D and a bone formation marker, osteocalcin (15, 16). Another study showed no significant effect on calcium-regulating hormones and bone remodeling in normocalcemic renal transplant recipients with good renal functions (17). The effect of immunosuppressants on bone turnover seems to depend largely on other factors modifying calcium metabolism and needs further investigation. A report has indicated that the blood concentration of cyclosporine is regulated by hepatic metabolism which seems to be modulated by estradiol (18). It remains of special interest how the posttransplantation acute hepatic failure modulated the bone turnover through affecting cyclosporine metabolism.

Recent studies have been unveiling the central pathways for the regulation of bone formation/resorption coupling: molecular interactions of receptor activator of nuclear factor kappa-B (RANK), the ligand for RANK (RANK-L), and osteoprotegerin, a decoy receptor of RANK-L. The differentiation and maturation of osteoclasts are highly dependent on the interaction of RANK expressed on the precursor cells and RANK-L expressed on osteoblasts and bone stromal cells (19). The depletion of T cells was reported to up-regulate osteoclastogenesis through an increased prostaglandin production (20). Thus, immunosuppressive agents may enhance osteoresorption by inhibiting T cells from intervening in the RANK-L signaling involved in osteoclastogenesis. The uncoupling of bone turnover as the basis for hypercalcemia in the present case was shown by the normal level of serum osteocalcin and the successful control of the hypercalcemia by bisphosphonate, which should have corrected the predominance of bone resorption. The pathogenesis for the hypercalcemia experienced in the present case may be explained, at least in some part, by enhanced osteoresorption, which might be caused by intense immunosuppressive therapy used to prevent graft rejection. Interestingly, to date literature on hypercalcemia following organ transplantation seems to be limited to the liver, despite the potential effects of immunosuppressive therapy on calcium metabolism. The mechanism of hypercalcemia in liver dysfunction and immunosuppression should be further elucidated.

Acute renal dysfunction which followed the aggravation of hypercalcemia was successfully suppressed by the intravenous administration of pamidronate. Hypercalcemia is known to cause non-oliguric renal impairment with reductions in concentrating ability and in animal models it causes a reduction in the glomerular filtration rate and Na⁺Cl⁻ transport in the thick ascending limb (21–23). Although the mechanism is not well defined, this pathologic state is reversible in mild cases and thus should be recognized early and therapeutically intervened. The present case supports the use of pamidronate for hypercalcemia-induced acute renal failure which is unresponsive to calcitonin treatment.

In closing, we encountered an instructive case of hypercalcemia associated with living-unrelated liver transplantation and hypercalcemia-induced acute renal failure. Although the true pathogenesis of the hypercalcemia was not clarified, altered bone metabolism under intense immunosuppressive therapy and liver dysfunction appeared to be an important therapeutic target. Special attention should be paid to post-liver transplantation hypercalcemia in terms of altered bone metabolism associated with liver dysfunction and immunosuppressive therapy for a more theoretical and effective treatment in the future.

References


